Genetically predicted insulin-like growth factor-I in relation to muscle mass and strength

Shuai Yuan¹ | Susanna C. Larsson¹,²

¹Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
²Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Abstract

Objective: Insulin-like growth factor I (IGF-I) has been associated with muscle status in animal- and population-based studies. We conducted a Mendelian randomisation study to assess the causality of the associations of IGF-I with muscle strength and mass.

Design and Patients: Genetic variants associated with serum IGF-I at genome-wide significance in the UK Biobank study (358,072 individuals of European descent) were selected as instrumental variables. Summary-level data on the associations of those variants with muscle weakness (low-grip strength) and muscle mass (fat-free body mass) were available from a meta-analysis of 22 genome-wide association studies including 46,596 cases and 209,927 noncases and genome-wide association analysis in 155,961 individuals from the UK Biobank study, respectively. The univariable and multivariable inverse-variance weighted methods were used.

Results: Higher genetically predicted IGF-I levels were associated with a reduced risk of muscle weakness and increased muscle mass. For one standard deviation increase in genetically predicted IGF-I levels, the odds ratio was 0.92 (95% confidence interval [CI], 0.88, 0.97; \( p = .001 \)) for muscle weakness and the change was 0.53 (95% CI: 0.28, 0.79; \( p < .001 \)) kg for muscle mass. In the multivariable model with adjustment for genetically predicted height, the associations were attenuated but persisted for both muscle weakness (odds ratio: 0.95, 95% CI: 0.91, 0.99; \( p = .015 \)) and muscle mass (change: 0.25, 95% CI: 0.10, 0.40; \( p = .001 \)).

Conclusion: This study suggests that high IGF-I levels may decrease the risk of muscle weakness and loss.

Keywords:
grip strength, insulin-like growth factor I, Mendelian randomisation, muscle mass, muscle weakness

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. Clinical Endocrinology published by John Wiley & Sons Ltd.
INTRODUCTION

Maintenance of muscle mass and strength is important for physical independence and life quality in community-dwelling older adults. Data from animal and observational population-based studies have shown that insulin-like growth factor I (IGF-I) may play a role in muscle growth and reduce the risk of muscle weakness and loss. However, whether these associations can be interpreted as causal relationships remains unestablished due to inconsistent findings, potential methodological limitations (e.g., residual confounding and reverse causation bias) in available studies, and the lack of data from randomised controlled trials. Considering the ageing population in most countries and areas, a clear appraisal of the causality of the association between IGF-I and muscle mass is important and could improve strategies to prevent muscle loss and weakness.

Leveraging genetic variants as instrumental variables for exposure (e.g., IGF-I), the Mendelian randomisation (MR) approach can strengthen the causal inference in an exposure-outcome association. The MR method can minimise residual confounding as genetic variants are randomly assorted at conception, and thus unassociated with environmental factors. In addition, the genetic variants cannot be modified by the onset and progression of the disease, which diminishes the risk of reverse causation bias. Here, we conducted an MR study to determine the associations of IGF-I with muscle strength (measured as grip strength) and muscle mass.

METHODS

2.1 Genetic instrument selection

Single nucleotide polymorphisms (SNPs) associated with serum IGF-I levels at the genome-wide significance level \( p < 5 \times 10^{-8} \) were obtained from a genome-wide association analysis in the UK Biobank study including 358,072 individuals of European descent. Age, sex and genetic principal components were adjusted for in the association tests. Linkage disequilibrium among these SNPs was calculated based on the 1000 Genomes European panel and defined as \( r^2 > 0.01 \) or distance less than 10,000 kb. A total of 416 SNPs without linkage disequilibrium were selected as instrumental variables for serum IGF-I (Table S1). The selected SNPs explain \( \sim 9.4\% \) of phenotypic variance and have been used in previous MR studies. In the UK Biobank, the mean ± standard deviation (SD) of IGF-I concentration is 21.4 ± 5.7 nmol/L and the IGF-I concentration in the first and ninth decile is 14.2 and 28.4 nmol/L, respectively. The effect sizes of SNPs associated with IGF-I were scaled to one SD change.

2.2 Data source for muscle weakness

Summary-level data for the associations between IGF-I-associated SNPs and muscle weakness (low-grip strength) were derived from a meta-analysis of 22 genome-wide association studies including 256,523 individuals of European ancestry aged 60 years and older. A total of 46,596 participants (18.9%) were defined as suffering from muscle weakness, defined by a grip strength less than 30 kg for men and less than 20 kg for women according to the 2010 European Working Group on Sarcopenia in Older People definition of low-grip strength. The SNP-muscle weakness estimates were adjusted for age, sex, population structure, relatedness and genotyping batch where applicable.

2.3 Data source for muscle mass and height

Whole-body fat-free mass was used as an indicator for muscle mass. The summary-level data for fat-free mass were obtained from a...
2.4 Statistical analysis

Given the sample overlap between the exposure data and outcome data (~78% for the analysis of muscle weakness and 100% for the analysis of muscle mass), the F statistics were calculated assuming the same variance in IGF-I explained by used SNPs in the outcome populations as in the population in the genome-wide association study of IGF-I. An F-statistic greater than 10 indicates a good strength of the genetic instrument and minimal bias introduced by sample overlap. As the main statistical approach, we used the random-effects inverse-variance weighted method, which can provide the most accurate estimate. Four sensitivity analyses, including the weighted median, MR-Egger, MR-PRESSO and contamination mixture methods, were performed to examine the consistency of the results and detect and correct for possible horizontal pleiotropic effects. Assuming at least 50% of the weight from valid instruments, the weighted median method can generate consistent causal estimates. We used the intercept in the MR-Egger regression to detect pleiotropy and obtain the estimates after the correction for pleiotropy. The MR-PRESSO analysis can distinguish outlying SNPs and provide causal estimates after the removal of identified outliers. The contamination mixture approach is a robust MR method that can identify groups of SNPs with similar causal estimates, which may represent separate mechanisms whereby the risk factor affects the outcome. We further performed a sensitivity analysis using an instrument consisting of 66 correlated SNPs (r² ≤ 0.4) located in the IGF1 gene region (genomic position on build GRCh37/hg19: chromosome 12:102789652–102874341) and associated with IGF-I levels at the genome-wide significance level. A matrix of linkage disequilibrium among these SNPs was introduced in the MR analysis model. Considering that height may exert pleiotropic or mediation effects, we used the multivariable MR analysis with the adjustment for genetically predicted height to investigate the independent causal effects of IGF-I on muscle weakness and mass. IGF-I associated SNPs may directly influence the risk of muscle weakness and mass, we performed a sensitivity analysis by excluding SNPs associated with the outcomes at the loci-wide significance level (p < 1 × 10⁻⁵). All tests were two-sided and performed using the TwoSampleMR, MR-PRESSO and MendelianRandomization packages in the R software (version 4.0.2).

3 RESULTS

The F-statistic was 64 in the analysis of muscle weakness and 39 in the analysis of muscle mass. Higher genetically predicted serum IGF-I levels were associated with a reduced risk of muscle weakness (Figure 2). For one SD increase in genetically predicted serum IGF-I, the odds ratio (OR) of muscle weakness was 0.92 (95% confidence interval [CI], 0.88, 0.97; p = .001) in the main analysis. The association remained consistent in all sensitivity analyses although with wider CIs in the weighted median and MR-Egger models. We observed moderate heterogeneity (Cochrane’s Q = 781.85) among estimates from used SNPs, but no horizontal pleiotropy was indicated by the intercept (p = .531) in the MR-Egger regression model. Four outlying SNPs were identified in the MR-PRESSO analysis, and the association became stronger (OR: 0.91, 95% CI: 0.87, 0.95; p < .001) after omitting these outliers. In the analysis excluding SNPs associated with muscle weakness at p < 1 × 10⁻⁵ (n = 2), the association remained (OR: 0.91, 95% CI: 0.87, 0.96; p < .001). The association remained directionally consistent in the sensitivity analysis based on SNPs located in the IGF1 gene region as instrumental variables (OR: 0.89, 95% CI: 0.75, 1.06; p = .200).

Higher genetically predicted IGF-I levels were associated with increased levels of muscle mass (Figure 3). The change of muscle mass was 0.53 (95% CI: 0.28, 0.79; p < .001) kg per one SD increase in genetically predicted IGF-I levels in the main analysis. Results remained consistent in the sensitivity analyses. We observed high heterogeneity (Cochrane’s Q = 7143.54) and possible pleiotropy (p for the intercept in MR-Egger = 0.041) but the association
4 DISCUSSION

The present MR study found that genetically predicted serum IGF-I was inversely associated with muscle weakness and positively associated with muscle mass. Approximately one-third of the effect of IGF-I on muscle mass appeared to be explained by height.

Our results supported the findings from most previous observational studies. A cohort study including 1292 Dutch community-dwelling older adults followed by 3 years found that elevated levels of IGF-I were associated with higher handgrip strength and superior physical performance. The positive association between IGF-I and muscle strength was also observed in a cross-sectional study in 526 Italians. In a cohort study in 1122 American older adults, IGF-I showed a borderline positive association with grip strength and lower levels of IGF-binding protein-1 were strongly associated with better handgrip strength. A cross-sectional study in 349 participants observed that IGF-I was associated with grip strength in obese individuals but not in nonobese individuals. The present MR study based on a large sample size strengthened the causal impact of IGF-I on muscle strength. An intervention study revealed that only individuals with IGF-I promoter polymorphisms achieved improvement in muscle strength after a 10-week strength training, which was in line with our finding and additionally indicated that IGF-I might mediate the effects of physical activity on muscle strength.

Evidence on the association of IGF-I with muscle mass is conflicting. A study including both young and elderly women found that IGF-I levels were positively correlated with muscle mass and the correlation was confirmed in a cross-sectional study including 3276 Chinese adults. In another cross-sectional study in 4908 Swedish women, IGF-binding protein-1 was inversely associated with muscle mass, which on the other hand, supported that ascended IGF-I levels were associated with more muscle mass. A cohort study including 1542 British women found that IGF-I levels were positively associated with lean body mass at the baseline; however, the change of IGF-I showed no association with lean body mass. In another cohort study with 232 men and 326 women followed by 3 years, higher IGF-I predicted smaller loss of muscle mass than lower IGF-I did in men but not in women. The present MR study found a consistent positive association between high genetically predicted IGF-I and muscle mass in different models and hinted at the causal potential of this association.

Underlying mechanisms that explain the association of IGF-I with muscle strength and mass have not been fully understood. IGF-I is an important regulator of muscle protein and glucose homeostasis. The absence of this channel was found to increase basal glucose uptake in muscle, which might influence the function of muscle cells. IGF-I has been shown to be able to increase the proliferation capacity of muscle satellite cells. Activated satellite cells can repair and regenerate damaged or myopathic skeletal muscle, thereby rescuing ageing-related or inactivity induced loss of muscle mass. In addition, IGF-I can reduce muscle loss by preventing excessive toxic-induced inflammatory expansion. The inhibition of myostatin by follistatin upon the IGF-I receptor/Akt/mTOR cascade has also been proved to induce dramatic skeletal muscle mass increases.

There are several strengths of the present study. The major strength is the MR design, which minimises residual confounding and other biases and reinforces the causal inference. The associations were examined using data from genome-wide association studies with large numbers of participants, and therefore we had a high power to detect even weak associations. The study population was confined to individuals of European descent and the association tests in the used genome-wide association studies were adjusted for principal genetic components. Thus, it was unlikely that population structure bias influenced our findings.

Several limitations deserve attention when interpreting our findings. First, population confinement might limit the generalisability of our results to other populations. Second, horizontal pleiotropy might bias our findings, especially for the analysis of muscle mass. However, high consistency across results from sensitivity analyses indicated that bias caused by horizontal pleiotropy was likely minimal. In addition, the associations for muscle mass and muscle weakness were replicated in the analyses based on SNPs located in the IGF1 gene region.
gene region. Third, the sample overlap might lead to model overfitting and inflated type 1 error rates, which could bias the causal estimates towards the observational estimates. Nevertheless, an F-statistic of more than 10 suggested that any bias introduced by sample overlap might not be an important issue in this study.20

Fourth, as this MR study was based on summary-level data, subgroup analysis could not be performed, such as within patients with endocrine diseases or with medications influencing body composition. Fifth, genetic variation results in lifelong exposure to varying IGF-I levels. Whether our findings can be generalised to populations with time-specific IGF-I treatments needs assessments. Sixth, autocrine/paracrine IGF-I plays an important role in tissue development and homeostasis throughout life and is, at least in part, independent of circulating IGF-I levels. 34,35 The independent effects of autocrine/paracrine IGF-I and its interaction with circulating IGF-I on muscle mass and strength need to be assessed in future study.

5 | CONCLUSION

In conclusion, this study suggests that high IGF-I levels may decrease the risk of muscle weakness and increase muscle mass. Previous evidence has also indicated a potential role of elevated IGF-I levels in fracture prevention.16 However, whether IGF-I treatment or certain lifestyle interventions to elevate IGF-I levels, such as increasing protein intake,36–38 deserves promotion for the prevention of fracture and muscle weakness and loss needs to be weighed against its possible adverse health effects, such as the increased risk of type 2 diabetes and colorectal cancer.15,17

ACKNOWLEDGEMENTS

This study is supported by the Swedish Research Council for Health, Working Life and Welfare (Forte; Grant No. 2018-00123) and the Swedish Research Council (Vetenskapsrådet; Grant No. 2019-00977). Genetic instruments for insulin growth factor 1 were obtained from the UK Biobank study. Genetic association estimates for muscle weakness and muscle mass were obtained from a published meta-analysis of 22 genome-wide association studies and genome-wide association analysis in the UK Biobank study, respectively. The authors thank all the investigators for sharing these data.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Susanna C. Larsson and Shuai Yuan designed the study and reviewed the manuscript. Shuai Yuan analysed the data, made the figures and drafted the manuscript. Both authors approved the final version of the manuscript.

ETHICS STATEMENT

All studies included in cited genome-wide association studies had been approved by a relevant review board. The present Mendelian randomisation analyses were approved by the Swedish Ethical Review Authority (2019-02793).

DATA AVAILABILITY

All data analysed in this study are available in Table S1.

ORCID

Shuai Yuan https://orcid.org/0000-0001-5055-5627
Susanna C. Larsson https://orcid.org/0000-0003-0118-0341

REFERENCES


SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.